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TABLE 2
Summary of gemifloxacin and comparator activity against
Streptococcus pneumoniae from *in vitro* profile studies

Compound	No. of Isolates	MIC Range (µg/mL)	Range of MIC ₉₀ s (µg/mL)	Median MIC ₉₀ (µg/mL)	References
<i>S. pneumoniae</i> (not differentiated)					
Gemifloxacin	185	≤0.008-0.06	0.03-0.06	0.03	[33] [36]
Clinafloxacin	100	0.03-0.25	0.12	NA ¹	[33]
Moxifloxacin	185	≤0.02-0.25	0.25	0.25	[33] [36]
Trovafoxacin	185	≤0.02-0.25	0.12	0.12	[33] [36]
Levofloxacin	185	0.12-2	1	1	[33] [36]
Ciprofloxacin	185	0.06-8	1-2	1	[33] [36]
<i>S. pneumoniae</i> (Pen-S)					
Gemifloxacin	261	≤0.004-0.25	0.03-0.06	0.06	[37] [35] [34] [39]
Moxifloxacin	196	0.06-0.25	0.25	0.25	[37] [39]
Trovafoxacin	261	≤0.008-1	0.12-0.25	0.25	[37] [35] [34] [39]
Levofloxacin	239	0.06-4	1-2	2	[35] [34] [39]
Ciprofloxacin	261	0.12-8	1-4	2	[37] [35] [34] [39]
<i>S. pneumoniae</i> (Pen-I)					
Gemifloxacin	72	≤0.008-0.12	0.03-0.12	0.03	[37] [35] [34] [39]
Moxifloxacin	39	0.06-0.25	0.12-0.25	0.12	[37] [39]
Trovafoxacin	72	≤0.03-0.5	0.12-0.5	0.25	[37] [35] [34] [39]
Levofloxacin	59	0.12-4	1-2	2	[35] [34] [39]
Ciprofloxacin	72	0.25-4	1-4	2	[37] [35] [34] [39]
<i>S. pneumoniae</i> (Pen-R)					
Gemifloxacin	51	≤0.004-1	0.03-0.12	0.03	[37] [35] [34]
Moxifloxacin	10	0.06-0.12	0.12	NA	[37]
Trovafoxacin	51	≤0.03->8	0.12->8	0.25	[37] [35] [34]
Levofloxacin	41	0.5->16	1->16	1	[35] [34]
Ciprofloxacin	51	0.25->8	1->8	1	[37] [35] [34]

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TABLE 2 (continued)
Summary of gemifloxacin and comparator activity against
Streptococcus pneumoniae from *in vitro* profile studies

Compound	No. of Isolates	MIC Range (µg/mL)	Range of MIC ₉₀ s (µg/mL)	Median MIC ₉₀ (µg/mL)	References
<i>S. pneumoniae</i> (Quin-S) ²					
Gemifloxacin	332	≤0.008-0.25	0.06	0.06	[32] ³ [40] ⁴
Clinafloxacin	125	0.06-0.25	0.12	NA	[32] ³
Trovafoxacin	332	0.016-1	0.25	0.25	[32] ³ [40] ⁴
Levofloxacin	332	0.12-4	2	2	[32] ³ [40] ⁴
Ciprofloxacin	207	0.25-4	4	NA	[40] ⁴
<i>S. pneumoniae</i> (Quin-R) ²					
Gemifloxacin	160	≤0.03-2	0.25-1	0.5	[32] ⁵ [38] ⁷ [40] ⁶
Clinafloxacin	57	0.25-4	1	NA	[32] ⁵
Moxifloxacin	75	0.12-8	4	NA	[32] ⁵ [38] ⁷ [40] ⁶
Trovafoxacin	160	0.25->8	4-8	4	[32] ⁵ [38] ⁷ [40] ⁶
Levofloxacin	160	0.5->32	16->32	>16	[32] ⁵ [38] ⁷ [40] ⁶
Ciprofloxacin	103	4->32	32->32	32	[38] ⁷ [40] ⁶

¹ NA = Not applicable—insufficient data to determine a median value

² defined in individual studies

³ Levofloxacin MIC ≤ 2 µg/mL

⁴ Ciprofloxacin MIC ≤ 4 µg/mL

⁵ Levofloxacin MIC ≥ 8 µg/mL

⁶ Ciprofloxacin MIC ≥ 8 µg/mL

⁷ Ciprofloxacin MIC ≥ 4 µg/mL

TABLE 3 shows the results of individual profile studies. In all of these studies gemifloxacin had low MIC values. The MIC₉₀ value was ≤0.06 µg/mL, except in studies that tested quinolone-resistant strains. In studies that tested quinolone-resistant strains the MIC₉₀ was 0.5-1.0 µg/mL (in the resistant category for gemifloxacin). The MIC₉₀ value for gemifloxacin was usually 2-fold lower than that of clinafloxacin and about 4- to 8-fold lower than that of moxifloxacin or gatifloxacin. Gemifloxacin's MIC₉₀ value was usually 32- to 64-fold better than that of levofloxacin or ciprofloxacin.

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TABLE 3
Activity of Gemifloxacin Against
Streptococcus pneumoniae (individual studies)

Compound	No. of Isolates	Country	MIC Range (µg/mL)	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)	Reference
Gemifloxacin	347	USA	0.004-0.06	0.016	0.03	[41]
Gemifloxacin	80	USA	≤0.004-1	0.015	0.03	[34]
Gemifloxacin	59	USA	0.008-0.03	0.03	0.03	[35]
Gemifloxacin	207	USA	≤0.008-0.25	0.03	0.06	[40]
Gemifloxacin	64 Pen-S		≤0.008-0.25	0.015	0.03	
	68 Pen-I		≤0.008-0.25	0.015	0.06	
	75 Pen-R		≤0.008-0.25	0.03	0.06	
	28 Cipro ≥ 8		0.03-1.0	0.25	0.25	
Gemifloxacin	182	N.A.	0.015-0.12	0.03	0.06	[32]
Gemifloxacin	57 Levo ≥8	EURO	0.06-2	0.25	0.25	
Gemifloxacin	85	Canada	≤0.02-0.06	0.03	0.06	[36]
Gemifloxacin	45	Canada	----	----	0.03	[37]
Gemifloxacin	75 Cipro ≥ 4	Canada	≤0.03-1	0.06	0.25	[38]
Gemifloxacin	174	Germany	----	0.03	0.06	[39]
Gemifloxacin	100	Italy	≤0.008-0.06	0.015	0.03	[33]
Gemifloxacin	134 E-test	Greece	0.002-0.25	0.03	0.06	[43]
Gemifloxacin	373 Pen-S	CMI	≤0.008-0.25	0.03	0.06	[31]
	93 Pen-I		0.016-0.12-	0.03	0.06	
	110 Pen-R		0.016-0.12	0.03	0.06	
Gemifloxacin	552	CAST	----	0.015	0.015	[30]
Gemifloxacin	2409	Global	0.001-128	0.015	0.03	[28]
	1515 Pen-S		----	0.015	0.03	
	521 Pen-I		----	0.015	0.03	
	372 Pen-R		----	0.015	0.03	
	78 Cip-R		0.008-128	0.06	0.25	

Shaded values are greater than the susceptible breakpoint for gemifloxacin.

Surveillance Studies

Table 4 and Table 5 show gemifloxacin MIC₅₀, MIC₉₀, and range for *Streptococcus pneumoniae* tested from The Global Gemifloxacin Surveillance Study (GGSS) (28), The Alexander Project (29), CAST (30), and CMI (31). The range of MIC₉₀s in the US/Canada was 0.015-0.06 µg/mL, and 0.03 µg/mL for all geographic regions.

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TABLE 4
In vitro Activity of Gemifloxacin against 3,005 *S. pneumoniae* from
Surveillance Studies (US/Canada)

Study	Number of Isolates	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)	MIC Range (µg/mL)
GGSS	421	0.015	0.03	0.004-2.0
Alexander Project	1,456	0.015	0.03	≤0.004-0.5
CAST	552	0.015	0.015	≤0.004-0.5
CMI	576	0.03	0.06	≤0.008-0.25

TABLE 5
In vitro Activity of Gemifloxacin against 7321 *S. pneumoniae* from
Surveillance Studies (All geographic regions)

Study	Number of Isolates	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)	MIC Range (µg/mL)
GGSS	2409	0.015	0.03	0.001-128.0
Alexander Project	4012	0.015	0.03	≤0.004-0.5
CAST	897	0.015	0.03	≤0.004-2.0

TABLE 6 shows the frequency distribution of gemifloxacin and comparator MICs for *Streptococcus pneumoniae* from surveillance studies in all geographic regions. TABLE 7 shows the frequency distribution for the US/Canada surveillance studies.

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TABLE 6
Frequency Distribution of MICs for *S. pneumoniae* in Surveillance Studies
(all geographic regions)

N/Cum%	0.001	0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	Total
Gemifloxacin	13 0.16	24 0.47	81 1.49	808 11.73	3984 62.18	2656 95.82	258 99.09	37 99.56	16 99.76	10 99.89	9 100*						7896
Ciprofloxacin					8 0.10	1 0.11	2 0.14	12 0.29	44 0.85	1007 13.61	4733 73.59	1858 97.14	225 100*				7891
Grepafloxacin					69 2.87	147 8.97	246 19.19	1213 69.56	668 97.30	44 99.13	4 99.29	4 99.46	4 99.63	4 99.79	2 99.88	3 100*	2408
Levofloxacin				1 0.03	12 0.37	2 0.42	10 0.71	10 0.99	60 2.69	1450 43.67	1905 97.51	61 99.24	6 99.41	21 100*			3538
Ofloxacin							20 0.31	4 0.37	11 0.55	28 0.98	1033 17.07	4989 94.78	302 99.49	33 100*			6420
Trovafoxacin				1 0.03	22 0.59	48 1.83	789 22.15	2401 83.98	553 98.22	29 98.97	14 99.33	2 99.38	14 99.77	9 100*			3883

* Highest concentration tested in one or more of the studies.

TABLE 7
Frequency Distribution of MICs for *S. pneumoniae* in Surveillance Studies
(US/Canada)

N/Cum%	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	Total
Gemifloxacin	28 0.84	381 12.33	1650 62.07	1114 95.66	115 99.13	11 99.46	9 99.73	5 99.88	4 100*				3317
Ciprofloxacin						2 0.06	11 0.29	414 12.87	2119 76.76	713 98.25	58 100*		3317
Grepafloxacin			5 1.19	2 1.66	30 8.79	230 63.42	146 98.10	5 99.29			3 100		421
Levofloxacin		1 0.03	4 0.32		1 0.39	1 0.45	12 1.29	462 31.08	1034 97.74	23 99.23	2 99.36	10 100*	1551
Ofloxacin							2 0.11	3 0.27	277 15.02	1532 96.64	57 99.68	6 100*	1877
Trovafoxacin		1 0.05	5 0.32	17 1.24	236 13.92	1212 79.04	358 98.28	13 98.98	4 99.19	1 99.25	13 99.95	1 100*	1861

* Highest concentration tested in one or more of the studies.

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Figures 1 and 2 show the *Streptococcus pneumoniae* gemifloxacin data from the surveillance studies in bar graphs. Figure 1 shows the data for the US/Canada studies and Figure 2 shows the data for all geographic regions.

Figure 1 Frequency distribution of gemifloxacin MICs for *S. pneumoniae* from surveillance studies - US/Canada (n = 3,317)

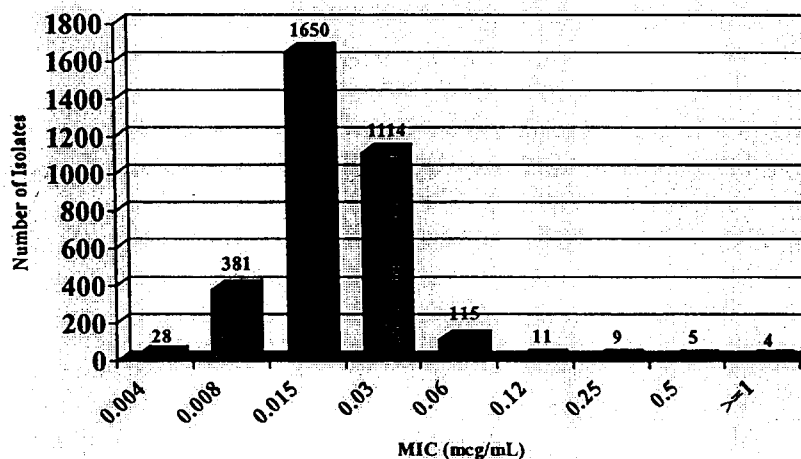
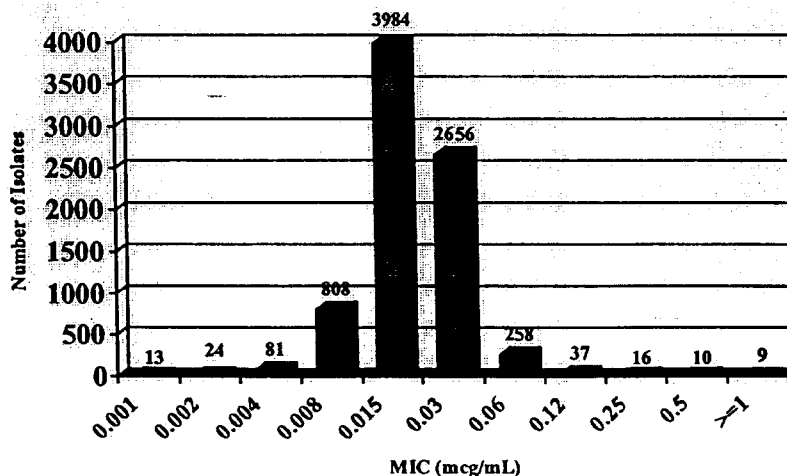


Figure 2 Frequency distribution of gemifloxacin MICs for *S. pneumoniae* from surveillance studies - all geographic regions (n = 7,896)



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Clinical data

This section contains frequency distributions of the gemifloxacin MICs for *Streptococcus pneumoniae* isolated from the Intent to Treat population during the Phase III clinical studies. The MIC₉₀ for the isolates recovered in North America was 0.015 µg/mL (TABLE 8), and 0.03 µg/mL for the isolates from all geographic regions (TABLE 9).

TABLE 8
Frequency Distribution of MICs for Gemifloxacin for *S. pneumoniae*
From the Phase III Clinical Studies (North America)

N=77	≤0.001	0.002	0.004	0.008	0.015	0.03
Gemi n	2	0	1	35	36	3
Cum %	2.6	2.6	3.9	49.4	96.1	100

TABLE 9
Frequency Distribution of MICs for Gemifloxacin for *S. pneumoniae*
From the Phase III Clinical Studies (all geographic regions)

N=386	≤0.001	0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25
Gemi n	6	4	1	65	258	48	1	2	1
Cum %	1.6	2.6	2.8	19.7	86.5	99.0	99.2	99.7	100

Discussion

The studies outlined above demonstrate that gemifloxacin has good activity against *Streptococcus pneumoniae*. In most studies gemifloxacin MIC₉₀s were 4-fold lower than the other quinolones tested. It must be remembered, however, that most other fluoroquinolones will have susceptible breakpoints that are at least 4 to 8 times higher than that for gemifloxacin. *Streptococcus pneumoniae* strains that have low-level resistance to levofloxacin and ciprofloxacin may still be susceptible to gemifloxacin. Gemifloxacin, like the other fluoroquinolones maintained its activity against penicillin-resistant and macrolide-resistant strains. *Streptococcus pneumoniae* will be allowed in the label. At the present time the Division is not allowing a claim in the label against macrolide-resistant *S. pneumoniae*. The Division believes that at the present time these strains are not a significant health risk. It will have to be determined whether enough patients infected with penicillin-resistant strains were cured to allow a claim for these strains. If this claim is allowed then *Streptococcus pneumoniae* (including penicillin-resistant strains) will be allowed in list #1 (clinical efficacy) in the microbiology subsection of the label. If this claim is not allowed then the microbiology subsection will list *Streptococcus pneumoniae* (penicillin-susceptible strains) in list #1 (clinical efficacy) and *Streptococcus pneumoniae* (penicillin-resistant strains) in list #2 (*in vitro* activity only).

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Other Gram-Positive Aerobes

To determine the activity of gemifloxacin against Gram-positive aerobes, other than *Streptococcus pneumoniae*, a number of *in vitro* susceptibility studies were conducted. Organisms tested included *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Staphylococcus aureus* (methicillin-susceptible and resistant strains), *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, and enterococci.

In vitro profile studies

Gemifloxacin demonstrated good *in vitro* activity against methicillin-susceptible staphylococci, including isolates resistant to erythromycin. As seen with other fluoroquinolones, activity was reduced against methicillin-resistant strains. Methicillin-resistant strains usually have MIC values in the resistant category. Gemifloxacin was active against *Streptococcus pyogenes*, but like other fluoroquinolones had high MIC values for enterococci. In all these studies gemifloxacin generally had MICs that were 2- to 4-fold lower than those of moxifloxacin and trovafloxacin and about 16- to 32-fold lower than those of levofloxacin or ciprofloxacin.

A summary of these studies is shown in TABLE 10.

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TABLE 10
Summary of gemifloxacin and comparator activity against
Aerobic Gram-positive organisms from *in vitro* profile studies

Compound	No. of Isolates	MIC Range (µg/mL)	Range of MIC ₉₀ s (µg/mL)	Median MIC ₉₀ (µg/mL)	References
<i>S. pyogenes</i>					
Gemifloxacin	265	≤0.004-0.06	0.03-0.06	0.03	[35] [33] [34]
Clinafloxacin	100	0.015-0.12	0.06	NA ¹	[33]
Moxifloxacin	100	0.06-0.5	0.25	NA	[33]
Trovaflaxacin	265	0.03-1	0.25	0.25	[35] [33] [34]
Levofloxacin	115	0.06-2	0.5-1	0.5	[35] [33]
Ciprofloxacin	265	0.12-2	0.5-1	1	[35] [33] [34]



<i>S. aureus</i> (not differentiated)					
Gemifloxacin	81	≤0.004-1	0.06-0.12	0.06	[36] [33]
Clinafloxacin	50	0.06-0.25	0.25	NA	[33]
Moxifloxacin	81	0.015-0.5	0.06-0.5	0.06	[36] [33]
Trovaflaxacin	81	≤0.004-0.5	0.03-0.25	0.03	[36] [33]
Levofloxacin	81	0.03-2	0.25-2	0.25	[36] [33]
Ciprofloxacin	81	0.06-4	1-4	1	[36] [33]
<i>S. aureus</i> (MSSA)					
Gemifloxacin	599	≤0.004-4	0.03-0.12	0.03	[34] [37] [43]
Moxifloxacin	42	≤0.008-1	0.12	NA	[37]
Trovaflaxacin	599	≤0.004-8	≤0.03-0.12	0.03	[34] [37] [43]
Ciprofloxacin	599	≤0.06-≥8	0.5-2	1	[34] [37] [43]
<i>S. aureus</i> (MSSA) CipS					
Gemifloxacin	15	0.008-0.06	0.06	NA	[35]
Trovaflaxacin	15	0.015-0.12	0.06	NA	[35]
Levofloxacin	15	0.12-0.5	0.5	NA	[35]
Ciprofloxacin	15	0.12-1	1	NA	[35]
<i>S. aureus</i> (MSSA) CipR					
Gemifloxacin	5	0.12-1	NA	NA	[35]
Trovaflaxacin	5	0.12-2	NA	NA	[35]
Levofloxacin	5	1-8	NA	NA	[35]
Ciprofloxacin	5	4-16	NA	NA	[35]

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TABLE 10 (continued)
Summary of gemifloxacin and comparator activity against
Aerobic Gram-positive organisms from *in vitro* profile studies

Compound	No. of Isolates	MIC Range (µg/mL)	Range of MIC ₉₀ s (µg/mL)	Median MIC ₉₀ (µg/mL)	References
<i>S. aureus</i> (MRSA)					
Gemifloxacin	447	0.008->16	4-8	8	[34] [37] [43]
Moxifloxacin	49	0.03-4	4	NA	[37]
Trovaflxacin	447	0.008->16	2-8	4	[34] [37] [43]
Ciprofloxacin	447	0.12->64	>8->16	>16	[34] [37] [43]
<i>S. aureus</i> (MRSA) CipS					
Gemifloxacin	10	0.015-0.06	0.06	NA	[35]
Trovaflxacin	10	0.03-0.06	0.06	NA	[35]
Levofloxacin	10	0.06-0.5	0.25	NA	[35]
Ciprofloxacin	10	0.25-1	1	NA	[35]
<i>S. aureus</i> (MRSA) CipR					
Gemifloxacin	10	0.5-4	2	NA	[35]
Trovaflxacin	10	1-8	4	NA	[35]
Levofloxacin	10	4-16	16	NA	[35]
Ciprofloxacin	10	8->16	>16	NA	[35]

TABLES 11 to TABLE 18 show the results of individual studies for *S. aureus*,
S. pyogenes,

Methicillin-susceptible strains of *S. aureus* are susceptible to gemifloxacin (MIC₉₀s = 0.06-0.12 µg/mL), but the MIC₉₀ value in studies testing methicillin-resistant strains (also ciprofloxacin-resistant) were in the resistant range.

Streptococcus pyogenes had MIC₉₀s of 0.015-0.12 µg/mL. This organism is associated with respiratory tract infections.

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The MIC₉₀ values for *Enterococcus faecalis* and *Enterococcus faecium* were in the resistant range for gemifloxacin. The MIC₉₀ values for *E. faecalis* were 2->16 µg/mL and the values were 4-64 µg/mL for *E. faecium*.

Viridans group streptococci were susceptible to gemifloxacin with MIC₉₀ values of 0.06-0.12 µg/mL. These organisms are not usually associated with the proposed indications.

The *Staphylococcus epidermidis* studies did not usually separate methicillin-susceptible and -resistant strains. The MIC₉₀ values, therefore, were variable and ranged from 0.015 to 2.0 µg/mL. This species is probably not a primary pathogen and is not associated with any of the proposed indications.

TABLE 11
Activity of Gemifloxacin Against
Staphylococcus aureus (individual studies)

Compound	No. of Isolates	Country	MIC Range (µg/mL)	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)	Reference
Gemifloxacin	50	Italy	≤0.004-0.12	0.06	0.12	[33]
Gemifloxacin	472 MS	USA	≤0.004-4	0.015	0.03	[34]
	355 MR		0.008-≥16	1.0	8.0	
Gemifloxacin	31	Canada	0.03-1	0.06	0.06	[36]
Gemifloxacin	10 MR Cip-R	USA	0.05-4	1.0	2.0	[35]
	10 MR Cip-S		0.015-0.06	0.03	0.06	
	5 MS Cip-R		0.12-1.0	0.25	---	
	15 MS Cip-S		0.008-0.06	0.03	0.06	
Gemifloxacin	85 MS	Greece	≤0.03-4	0.06	0.125	[43]
	43 MR		≤0.03-8	2.0	8.0	
Gemifloxacin	40 ER-S MS	Korea	≤0.008-0.12	0.015	0.06	[51]
	28 ER-R MS		≤0.008-0.06	0.015	0.06	
	1 MR ER-S		>32	---	---	
	21 MR ER-R		≤0.008-≥32	4.0	≥32	
Gemifloxacin	69 MS	USA	0.008-16	0.015	0.03	[50]
	72 MR		0.015-16	2.0	8.0	
Gemifloxacin	47 MS	Korea	≤0.008-0.13	0.03	0.06	[52]
	49 MR		≤0.008-4	0.03	1.0	
Gemifloxacin	20 MS	Korea	≤0.008-0.06	0.03	0.06	[53]
	20 MR		0.03->8	1.0	8.0	
Gemifloxacin	346 MS Cip-S	CMI	≤0.008-0.06	0.016	0.03	[31]
	29 MS Cip-R		0.03->16	0.5	8.0	
	13 MR Cip-S		≤0.008-0.5	0.016	0.06	
	160 MR Cip-R		0.06-16	2.0	16.0	
Gemifloxacin	199	CAST	---	≤0.03	2.0	
Gemifloxacin	4012	Alex Proj	≤0.004-0.5	0.015	0.03	[29]

Shaded values are above gemifloxacin susceptible breakpoint

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TABLE 12
Activity of Gemifloxacin Against

TABLE 13
Activity of Gemifloxacin Against

TABLE 14
Activity of Gemifloxacin Against
Streptococcus pyogenes (individual studies)

Compound	No. of Isolates	Country	MIC Range (µg/mL)	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)	Reference
Gemifloxacin	100 [60 ER-R]	Italy	≤0.004-0.06	0.015	0.03	[33]
Gemifloxacin	150	USA	≤0.004-0.06	0.015	0.03	[34]
Gemifloxacin	15	USA	0.015-0.06	0.03	0.06	[35]
Gemifloxacin	20	USA	≤0.004-0.03	0.015	0.015	[46]
Gemifloxacin	38 [7 ER-R]	Korea	0.016-0.12	0.03	0.06	[51]
Gemifloxacin	54	USA	0.008-0.06	0.016	0.03	[50]
Gemifloxacin	50	UK	≤0.008-0.12	0.03	0.06	[54]
Gemifloxacin	19	Korea	0.016-0.06	0.016	0.03	[52]
Gemifloxacin	20	Korea	0.016-0.12	0.03	0.12	[53]
Gemifloxacin	238	CMI	≤0.008-0.12	0.03	0.06	[31]
Gemifloxacin	770	Global	0.001-256	0.015	0.03	[28]

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Compound	No. of Isolates	Country	MIC Range (µg/mL)	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)	Reference
Gemifloxacin	404 Vanco-S	USA	≤0.03-≥16	0.125	1.0	[34]
Gemifloxacin	26 Vanco-R		≤0.03-≥16	1.0	1.0	
Gemifloxacin	15 Vanco-S	USA	0.03-4	0.25	1.0	[35]
	15 Vanco-R		0.03-4	2.0	2.0	
Gemifloxacin	81	Greece	0.03-≥32	0.25	16	[43]
Gemifloxacin	81	USA	0.03-16	0.06	2.0	[50]
Gemifloxacin	39	Korea	0.06-4.0	0.12	1.0	[52]
Gemifloxacin	15	Korea	0.06-4.0	0.25	1.0	[53]
Gemifloxacin	377 Vanco-S	CMI	0.016->16	0.06	1.0	[31]
	10 Vanco-R		2->16	16	≥16	
Gemifloxacin	921	Global	0.004-256	0.06	1.0	[28]

Shaded values are above gemifloxacin susceptible breakpoint

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3.1.1.1. The 1990s Generation: Entrepreneurial Mindset

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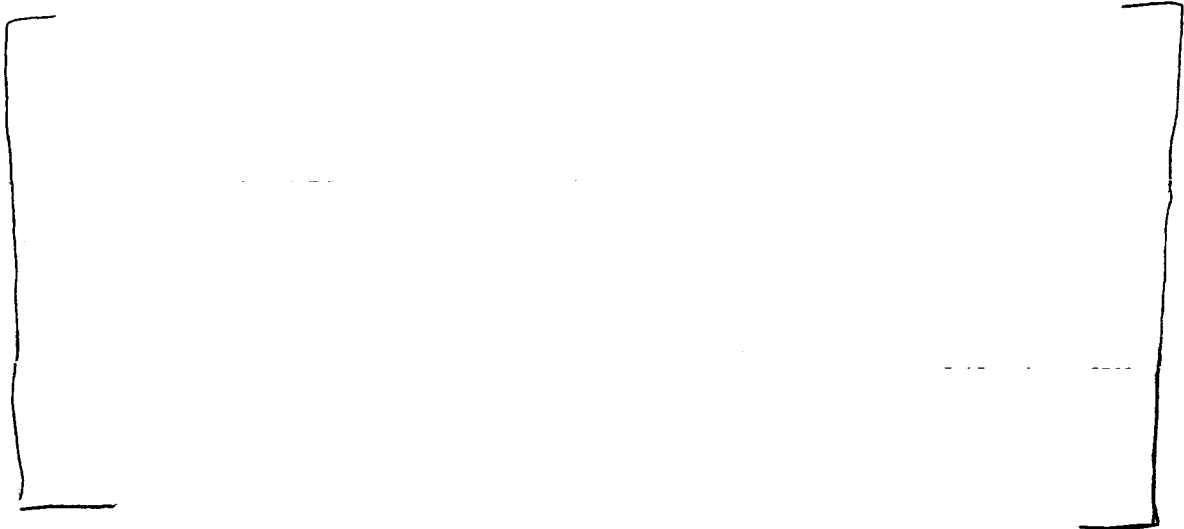
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TABLE 18
Activity of Gemifloxacin Against



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Surveillance Studies

TABLE 19 and TABLE 20 show gemifloxacin MIC₅₀, MIC₉₀, and range for *Streptococcus pyogenes*, _____ and _____ tested from The Global Gemifloxacin Surveillance Study (GGSS) (28), CAST (30), and CMI (31). The range of MIC₉₀s for the US/Canada isolates was ≤0.03-0.12 µg/mL, and ≤0.03-0.06 µg/mL for all geographic regions for *Streptococcus pyogenes* and _____. The range of MIC₉₀s for MSSA (excluding the ciprofloxacin-resistant isolates), and _____ was 0.015-0.12 µg/mL for the US/Canada, and ≤0.03-0.06 µg/mL for all geographic regions. Gemifloxacin's MICs against MRSA, ciprofloxacin-resistant MSSA, _____ were all well above the proposed susceptible breakpoint.

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TABLE 19
In vitro Activity of Gemifloxacin against Gram-Positive
Isolates from Surveillance Studies—US/Canada

Organism	Study	Number of Isolates	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)	MIC Range (µg/mL)
<i>Streptococcus Pyogenes</i>	GGSS	119	0.015	0.03	0.001-1.0
	CAST	33	≤0.03	≤0.03	≤0.03-0.06
	CMI	238	0.03	0.06	≤0.008-0.12
<i>Staphylococcus aureus</i> (MSSA)	GGSS	196	0.015	0.12	0.001-16
	CAST	734	≤0.03	≤0.03	≤0.03->4.0
	CMI (Cipro-S)	346	0.016	0.03	≤0.008-0.06
	CMI (Cipro-R)	29	0.5	8.0	0.03->16.0
<i>Staphylococcus Aureus</i> (MRSA)	GGSS	132	4.0	8.0	0.004-16.0
	CAST	506	2.0	>4.0	≤0.03->4.0
	CMI (Cipro-S)	13	0.016	0.06	≤0.008-0.5
	CMI (Cipro-R)	160	2.0	16.0	0.06-16.0

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<i>Enterococcus faecalis</i>	GGSS	131	0.06	2.0	0.008-64.0
	CAST	156	0.06	2.0	≤0.03->4.0
	CMI (Cipro-S)	377	0.06	4.0	0.016->16.0
	CMI (Cipro-R)	10	16.0	>16.0	2.0->16.0

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TABLE 20
In vitro Activity of Gemifloxacin against Gram-Positive
Isolates from Surveillance Studies—All geographic Regions

Organism	Study	Number of Isolates	MIC ₅₀ (μg/mL)	MIC ₉₀ (μg/mL)	MIC Range (μg/mL)
<i>Streptococcus pyogenes</i>	GGSS	770	0.015	0.03	0.001-256
	CAST	35	≤0.03	≤0.03	≤0.03-0.06
<i>Staphylococcus aureus</i> (MSSA)	GGSS	842	0.015	0.06	0.001-16
	CAST	860	≤0.03	≤0.03	≤0.03->4
<i>Staphylococcus aureus</i> (MRSA)	GGSS	764	1.0	8.0	0.001-128
	CAST	579	2.0	>4	<0.03->4
<i>Enterococcus faecalis</i>	GGSS	921	0.06	4.0	0.004-256
	CAST	206	0.06	2.0	≤0.03->4

NA = Not applicable—MIC₉₀ data not presented where number of isolates less than 10

TABLES 21 to TABLE 28 show the frequency distribution of gemifloxacin and comparator MICs for *S. pyogenes*, MSSA, MRSA, *E. faecalis*, and . The tables present the data combined from all three surveillance studies. Only the data from all geographic regions is shown.

Gemifloxacin had the lowest MICs of the tested quinolones against *S. pyogenes*; the MIC₉₀ was 0.03 μg/mL for the US/Canada and all geographic regions, at least 4-fold lower than the other quinolones. Gemifloxacin also had MIC₉₀ values at least 4-fold lower than the other quinolones against . streptococci. Gemifloxacin's MIC₉₀ was at least 2-fold lower against MSSA than that of the other quinolones tested. Against MSSA, trovafloxacin's and grepafloxacin MIC₉₀ values were only one dilution greater than that of gemifloxacin. Although all these drugs had good activity, trovafloxacin and grepafloxacin may be more active based on a breakpoint that is 8-16 fold greater than that of gemifloxacin's. All quinolones demonstrated poor activity against MRSA and *E. faecalis*. Since gemifloxacin's susceptible breakpoint will likely be at least 4-fold lower than most other quinolones its activity against most gram-positive aerobes will be at least equivalent and perhaps even better than that of the other tested quinolones (ciprofloxacin, grepafloxacin, levofloxacin, ofloxacin, and trovafloxacin).

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TABLE 21
Frequency Distribution of MICs for *S. pyogenes* in Surveillance Studies
(all geographic regions)

N/Cum%	0.001	0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	Total
Gemifloxacin	5 0.44	13 1.59	33 4.51	148 17.61	558 66.99	314 94.78	48 99.03	6 99.56	1 99.65		1 99.73		1 99.82	2 100*			1130
Ciprofloxacin					2 0.18	2 0.35	4 0.71	37 3.98	214 22.92	686 83.63	113 93.63	61 99.03	11 100*				1130
Grepafloxacin					14 1.83	37 6.65	67 15.38	272 50.85	271 86.18	82 96.87	18 99.22	4 99.74			1 99.87	1 100*	767
Levofloxacin					1 0.10	2 0.30	7 0.99	12 2.18	225 24.50	650 88.99	76 96.53	34 99.90		1 100*			1008
Ofloxacin							8 0.90	3 1.24	11 2.47	102 13.93	572 78.20	155 95.62	36 99.66	3 100*			890
Trovafoxacin					25 2.48	81 10.50	428 52.87	386 91.09	42 95.25	44 99.60	3 99.90			1 100*			1010

* Highest concentration tested in one or more of the studies.

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TABLE 22
Frequency Distribution of MICs for *Staphylococcus aureus* (Meth-S) in Surveillance Studies
(all geographic regions)

N/Cum%	0.001	0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	Total
Gemifloxacin	9 1.07	7 1.90	31 5.58	226 32.42	315 69.83	156 88.36	29 91.81	11 93.11	3 93.47	21 95.96	19 98.22	3 98.57	5 99.17	7 100*			842
Ciprofloxacin					2 0.24	2 0.48	27 3.68	138 20.07	285 53.98	254 84.09	52 90.26	19 92.52	63 100*				842
Grepafloxacin					65 7.72	297 42.99	299 78.50	100 90.38	19 92.64	6 93.35	4 93.82	2 94.06	2 94.30	10 95.49	19 97.74	19 100*	842
Levofloxacin					4 0.48	2 0.71	76 9.74	436 61.52	207 86.10	47 91.69	13 93.23	7 94.06	25 97.03	25 100*			842
Ofloxacin							7 0.83	46 6.29	359 48.93	304 85.04	50 90.97	17 92.99	9 94.06	50 100*			842
Trovafloxacin					473 56.24	221 82.62	45 87.87	29 91.32	7 92.15	13 93.70	32 97.50	5 98.10	4 98.57	12 100*			841

* Highest concentration tested in one or more of the studies.

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TABLE 23
Frequency Distribution of MICs for *Staphylococcus aureus* (Meth-R) in Surveillance Studies
(all geographic regions)

N/Cum%	0.001	0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	Total
Gemifloxacin	1 0.13	2 0.39	9 1.57	27 5.10	61 13.09	33 17.41	12 18.98	17 21.20	12 22.77	127 39.40	170 61.85	105 75.39	94 87.70	94 100*			764
Ciprofloxacin					2 0.26	3 0.65	4 1.18	25 4.45	50 10.99	35 15.58	13 17.28	10 18.59	622 100*				764
Grepafloxacin					9 1.18	51 7.85	53 14.79	19 17.28	11 18.72	4 19.24	14 21.07	3 21.47	5 22.12	32 26.31	304 66.10	259 100*	764
Levofloxacin						2 0.26	16 2.36	79 12.70	28 16.36	16 18.46	19.50	22.38	50.65	100*			764
Ofloxacin							3 0.29	11 1.83	47 7.98	63 16.23	11 17.67	10 18.98	25 22.25	594 100*			764
Trovafoxacin					74 9.70	38 14.68	13 16.38	14 18.22	12 19.79	47 25.95	241 57.54	167 79.42	98 92.27	59 100*			763

* Highest concentration tested in one or more of the studies.

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TABLE 26
Frequency Distribution of MICs for *Enterococcus faecalis* in Surveillance Studies
(all geographic regions)

N/Cum%	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	Total
Gemifloxacin	2 0.13	10 0.79	41 3.50	291 22.72	574 60.63	109 67.83	18 69.02	18 70.21	80 75.50	191 88.11	103 94.91	77 100*			1514
Ciprofloxacin			2 0.13	3 0.33	1 0.40	2 0.53	23 2.05	250 18.56	639 60.77	115 68.36	479 100*				1514
Grepafloxacin			2 0.22	7 0.98	22 3.37	95 13.70	349 51.63	149 67.83	17 69.67	10 70.76	26 73.59	23 76.09	122 89.35	98 100*	920
Levofloxacin			1 0.08	3 0.31	2 0.46	2 0.61	16 1.83	196 16.82	588 61.77	93 68.88	11 69.72	396 100*			1308
Ofloxacin					2 0.22	2 0.43	2 0.65	13 2.06	103 13.25	433 60.26	91 70.14	275 100*			921
Trovafoxacin			3 0.20	8 0.75	26 2.45	316 23.33	592 62.46	85 68.08	20 69.40	32 71.51	99 78.06	332 100*			1513

* Highest concentration tested in one or more of the studies.

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Figures 3 to 10 show the gemifloxacin data from the surveillance studies for *S. pyogenes*, MSSA, MRSA, *E. faecalis*, and . Only the data from all geographic regions combined is shown.

Figure 3—Frequency Distribution of gemifloxacin MICs for *S. pyogenes*
From surveillance studies—all geographic regions (n=1,130)

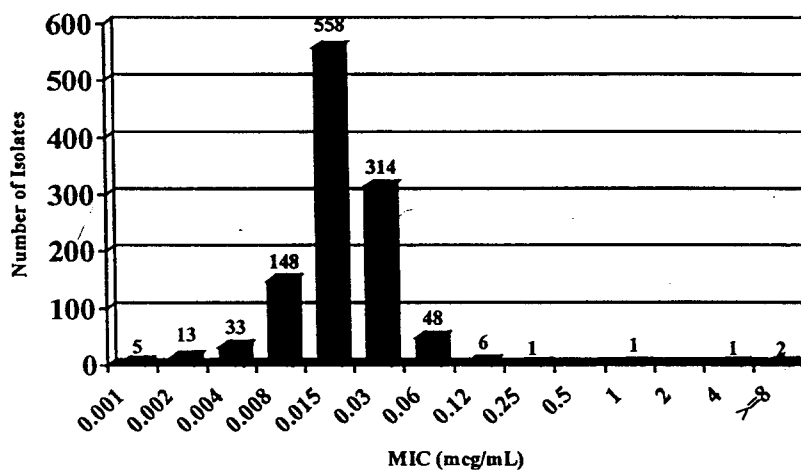
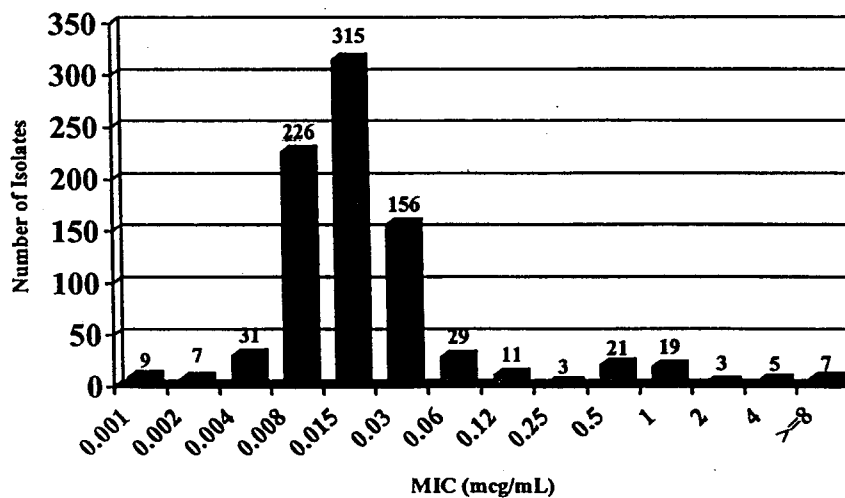


Figure 4—Frequency distribution of gemifloxacin MICs for *S. aureus* (MSSA)
From surveillance studies—all geographic regions (n=842)



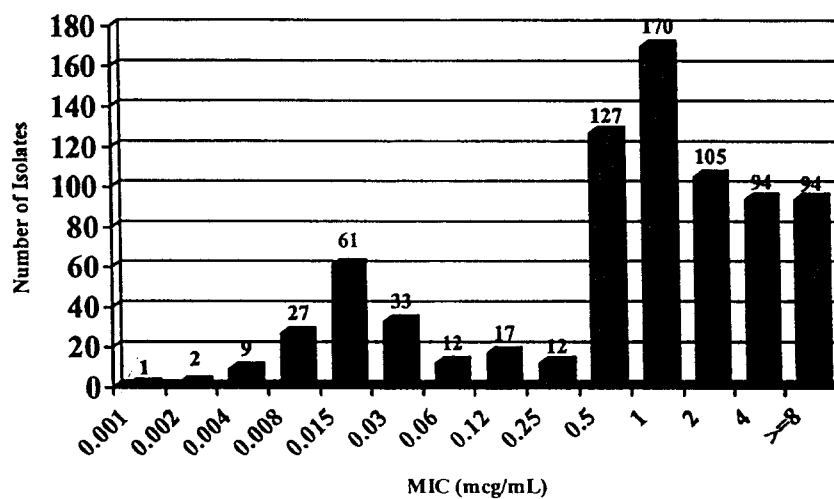
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Figure 5—Frequency distribution of gemifloxacin MICs for *S. aureus* (MRSA)
From surveillance studies—all geographic regions (n=764)



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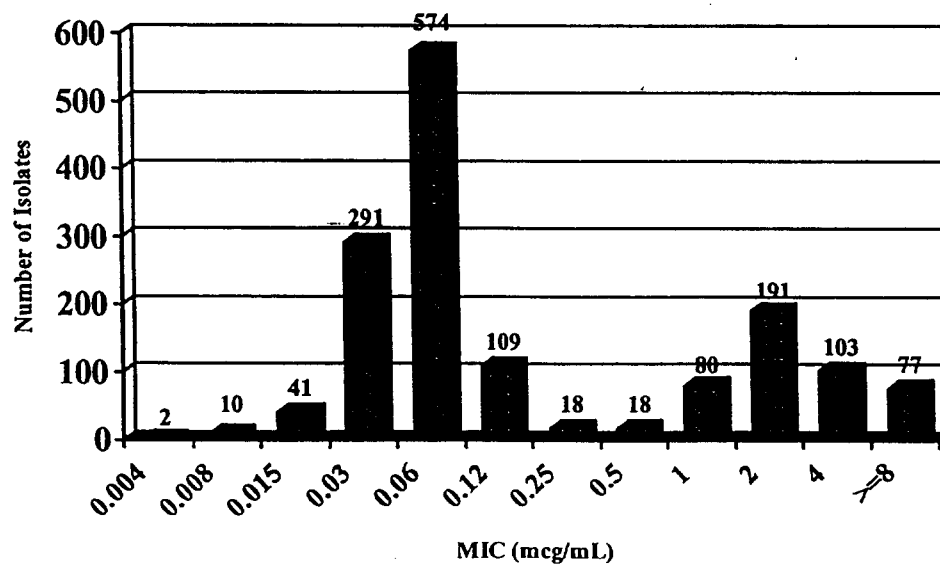
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Figure 8—Frequency distribution of gemifloxacin MICs for *E. faecalis*
From surveillance studies—all geographic regions (n = 1,514)



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Clinical data

This section contains frequency distributions of the gemifloxacin MICs for the Gram-positive organisms isolated from the Intent to Treat population during the Phase III clinical studies. The MIC₉₀ for MSSA isolates recovered in North America and from all geographic regions was 0.015 µg/mL. The MIC₉₀ for MRSA from all geographic regions was 8 µg/mL. There were only four isolates of MRSA recovered in North America.

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TABLE 29
Frequency Distribution of MICs for Gemifloxacin for *S. aureus* (meth-S)
From the Phase III Clinical Studies (North America)

N=70	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16
Gemi n	3	43	20	2	0	0	0	0	1	0	0	0	1
Cum %	4.3	65.7	94.3	97.1	97.1	97.1	97.1	97.1	98.6	98.6	98.6	98.6	100

TABLE 30
Frequency Distribution of MICs for Gemifloxacin for *S. aureus* (meth-S)
From the Phase III Clinical Studies (all geographic regions)

N=136	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16
Gemi n	7	74	46	5	1	0	0	0	1	1	0	0	1
Cum %	5.1	59.6	93.4	97.1	97.8	97.8	97.8	97.8	98.5	99.3	99.3	99.3	100

TABLE 31
Frequency Distribution of MICs for Gemifloxacin for *S. aureus* (meth-R)
From the Phase III Clinical Studies (all geographic regions)

N=12	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>256
Gemi n	1	1	1	3	2	0	2	1	0	0	0	0	1
Cum %	8.3	16.7	25.0	50.0	66.7	66.7	83.3	91.7	91.7	91.7	91.7	91.7	100

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Discussion

The studies outlined above demonstrate that gemifloxacin has good activity against methicillin-susceptible *Staphylococcus aureus*. The MIC₉₀ value is in the range of 0.06-0.12 µg/mL. Like other fluoroquinolones it has poor activity against methicillin-resistant strains. From the frequency distribution of MICs it appears that most methicillin-susceptible strains have MICs ≤ 0.12 µg/mL and most methicillin-resistant strains have MICs ≥ 0.5 µg/mL. The distribution for _____ is bipolar as is the distribution for _____ (data not shown). This is probably due to the non-separation of methicillin-susceptible and methicillin-resistant strains. These strains were not differentiated for these two species in most studies. Using these data setting a susceptible breakpoint of ≤ 0.12 µg/mL for staphylococci may be appropriate.

Staphylococcus aureus (methicillin-susceptible strains only) may be placed in the label. _____

_____ The overall MIC₉₀ value for _____ is 1.0 µg/mL, which is greater than the susceptible breakpoint.

The MIC₉₀ value for _____ is 0.03 µg/mL. Almost 300 isolates were tested. Over 80 isolates were from North America. Isolates were tested in more than one study. _____

The MIC₉₀ value for *Streptococcus pyogenes* is 0.03 µg/mL. Over 700 isolates were tested. Over 100 isolates were from North America. *Streptococcus pyogenes* may be listed in the *in vitro* activity list.

The MIC₉₀ value for _____ is 0.06 µg/mL. Over 800 isolates were tested; over 300 were from North America. _____

The MIC₉₀ value for _____ is 0.06 µg/mL. Over 560 isolates were tested; over 170 were from North America. _____

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GRAM-NEGATIVE AEROBES

This section contains an overview of the *in vitro* activity of gemifloxacin against Gram-negative aerobes. A primary indication for gemifloxacin will be respiratory tract infections, therefore, there is a particular focus on *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and *Moraxella catarrhalis*.

Haemophilus influenzae, *Haemophilus parainfluenzae*, and *Moraxella catarrhalis*

Gemifloxacin has very low MIC values against *Haemophilus* species and *Moraxella catarrhalis*. A number of *in vitro* profile and surveillance studies showed that the MICs for gemifloxacin are similar to those of the newer quinolones (MIC range ≤ 0.004 - $0.06 \mu\text{g/mL}$). The following section summarizes these studies and presents *Haemophilus* species and *Moraxella catarrhalis* data from the international surveillance studies, in addition to susceptibility data from the Phase III clinical studies.

In vitro profile studies

Early exploratory studies found that gemifloxacin demonstrated excellent *in vitro* activity against *H. influenzae*, *H. parainfluenzae*, and *M. catarrhalis*. Gemifloxacin maintained activity (as does other quinolones) against beta-lactamase producing strains, and isolates of *H. influenzae* resistant to erythromycin (45, 46, 47, 48). These findings were confirmed in more extensive studies. A summary of these results is shown in TABLE 32.

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TABLE 32
Summary of gemifloxacin and comparator activity against
H. influenzae, *H. parainfluenzae*, and *M. catarrhalis* from in vitro profile studies

Compound	No. of Isolates	MIC Range (µg/mL)	Range of MIC ₉₀ s (µg/mL)	Median MIC ₉₀ (µg/mL)	References
<i>H. influenzae</i> (not differentiated)					
Gemifloxacin	492	≤0.004-0.06	≤0.008-0.03	≤0.015	[36] [33] [34] [49] [43]
Clinafloxacin	100	≤0.008-0.06	≤0.008	NA ¹	[33]
Moxifloxacin	145	≤0.008-0.12	0.06	0.06	[36] [33]
Trovafoxacin	492	≤0.008-0.25	0.015-0.06	0.03	[36] [33] [34] [49] [43]
Levofloxacin	440	≤0.008-0.5	≤0.015-0.03	0.03	[36] [33] [49] [43]
Ciprofloxacin	445	≤0.008-0.5	0.008-0.015	0.015	[36] [33] [34] [49]
<i>H. parainfluenzae</i> (not differentiate)					
Gemifloxacin	10	≤0.015-0.12	0.12	NA	[36]
Moxifloxacin	10	0.06-0.5	0.5	NA	[36]
Trovafoxacin	10	≤0.015-0.12	0.12	NA	[36]
Levofloxacin	10	0.03-0.25	0.25	NA	[36]
Ciprofloxacin	10	≤0.015-0.06	0.06	NA	[36]
<i>M. catarrhalis</i>					
Gemifloxacin	145	≤0.004-0.03	≤0.015-0.015	0.015	[36] [33] [49]
Moxifloxacin	95	≤0.004-0.12	0.06	0.06	[36] [33]
Trovafoxacin	145	≤0.004-0.06	0.03-0.06	0.03	[36] [33] [49]
Levofloxacin	145	≤0.004-0.12	0.03-0.06	0.06	[36] [33] [49]
Ciprofloxacin	145	≤0.004-0.25	0.03	0.03	[36] [33] [49]

1 NA = Not applicable—insufficient data to determine a median value

TABLE 33 shows the results of individual profile studies for *Haemophilus influenzae*. TABLE 34 shows the results of individual profile studies for *Haemophilus parainfluenzae*. TABLE 35 shows the results of individual profile studies for *Moraxella catarrhalis*. In all studies gemifloxacin MICs were very low and were in the susceptible range. As usual for fluoroquinolones the MIC₉₀ values were higher for *H. parainfluenzae* as compared to *H. influenzae*. Strains that were β-lactamase positive were as susceptible as those that were β-lactamase negative.

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TABLE 33
Activity of Gemifloxacin Against
Haemophilus influenzae (individual studies)

Compound	No. of Isolates	Country	MIC Range (µg/mL)	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)	Reference
Gemifloxacin	100	Italy	≤0.008-0.06	≤0.008	≤0.008	[33]
Gemifloxacin	52	USA	≤0.0005-0.06	0.008	0.03	[34]
Gemifloxacin	45	Canada	≤0.02-0.03	≤0.02	≤0.02	[36]
Gemifloxacin	20 beta -	USA	0.015-0.12	0.03	0.06	[35]
	16 beta - AmpR		0.008-0.06	0.06	0.06	
	30 beta +		0.015-0.06	0.03	0.06	
Gemifloxacin	47	Greece	≤0.015	≤0.015	≤0.015	[43]
Gemifloxacin	20 beta -	USA	≤0.004	≤0.004	≤0.004	[46]
	20 beta +		≤0.004	≤0.004	≤0.004	
	19 beta - ampR		≤0.004	≤0.004	≤0.004	
Gemifloxacin	105 Cip-S	USA	≤0.002-0.25	≤0.002	0.008	[48]
	57 amp-R		≤0.002-1	≤0.002	0.03	
	20 ER-R		≤0.002-1	≤0.002	0.12	
Gemifloxacin	7	Korea	0.008-0.03	0.016	---	[52]
Gemifloxacin	271	USA	≤0.008-0.06	---	≤0.008	[47]
Gemifloxacin	101 beta +	USA	0.004-0.06	0.008	0.016	[49]
	147 beta -		0.004-0.03	0.008	0.016	
	9 Quin-R		0.03-1	0.25	---	
Gemifloxacin	86 beta +	CMI	≤0.008-0.016	≤0.008	0.016	[31]
	207 beta -		≤0.008-2	≤0.008	0.016	
Gemifloxacin	655	CAST	---	≤0.004	≤0.004	[30]
Gemifloxacin	4187	Alex Proj	≤0.008-0.5	≤0.008	0.03	[29]
Gemifloxacin	1817	Global	0.001-1	0.004	0.008	[28]

TABLE 34
Activity of Gemifloxacin Against
Haemophilus parainfluenzae (individual studies)

Compound	No. of Isolates	Country	MIC Range (µg/mL)	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)	Reference
Gemifloxacin	10	Canada	≤0.02-0.12	0.06	0.12	[36]
Gemifloxacin	26	USA	≤0.008-0.06	0.016	0.03	[47]
Gemifloxacin	101	CMI	≤0.008-4	0.016	0.06	[31]
Gemifloxacin	320	Global	0.001-0.12	0.015	0.03	[28]

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TABLE 35
Activity of Gemifloxacin Against
Moraxella catarrhalis (individual studies)

Compound	No. of Isolates	Country	MIC Range (µg/mL)	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)	Reference
Gemifloxacin	50	Italy	≤0.004-0.03	0.015	0.015	[33]
Gemifloxacin	45	Canada	≤0.02-0.03	≤0.02	≤0.02	[36]
Gemifloxacin	9 beta -	USA	≤0.008-0.016	≤0.008	≤0.008	[35]
	6 beta +		≤0.008-0.03	≤0.008	≤0.008	
Gemifloxacin	8 beta -	USA	≤0.004-0.008	≤0.004	—	[46]
	20 beta +		≤0.004-0.008	0.008	0.008	
Gemifloxacin	100	USA	≤0.002-0.016	0.004	0.008	[48]
Gemifloxacin	184	USA	0.004-0.016	0.008	0.008	[55]
Gemifloxacin	50	USA	0.008-0.03	0.016	0.016	[49]
Gemifloxacin	163 beta +	CMI	≤0.008-0.03	≤0.008	≤0.008	[31]
	18 beta -		≤0.008-0.016	≤0.008	≤0.008	
Gemifloxacin	263	CAST	—	≤0.004	0.008	[30]
Gemifloxacin	633	Alex Proj	≤0.008-0.5	≤0.008	0.015	[29]
Gemifloxacin	699	Global	0.001-0.12	0.008	0.015	[28]

Surveillance Studies

TABLE 36 and TABLE 37 show gemifloxacin MIC₅₀, MIC₉₀, and range for *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and *Moraxella catarrhalis* isolates tested from the Global Gemifloxacin Surveillance Study (GGSS) (28), The Alexander Project (29), CAST (30), and CMI (31). The range of MIC₉₀s for *H. influenzae* in the US/Canada was ≤0.004-0.016 µg/mL and ≤0.004-0.03 µg/mL for all geographic regions. The range of MIC₉₀s for *H. parainfluenzae* in the US/Canada was 0.03-0.06 µg/mL and 0.03 µg/mL for all geographic regions. The range of MIC₉₀s for *Moraxella catarrhalis* in the US/Canada was ≤0.008-0.015 µg/mL and 0.015 µg/mL for all geographic regions.

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TABLE 36
In vitro Activity of Gemifloxacin against *H. influenzae*, *H. parainfluenzae*
and *M. catarrhalis* Isolates from Surveillance Studies—US/Canada

Organism	Study	Number of Isolates	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)	MIC Range (µg/mL)
<i>Haemophilus influenzae</i>	(GGSS)	316	0.008	0.008	0.001-0.06
	Alexander Project	1370	0.008	0.008	0.008-0.06
	CAST	655	≤0.004	≤0.004	≤0.004-0.015
	CMI (β-lactamase positive)	86	≤0.008	0.016	≤0.008-0.016
	CMI (β-lactamase negative)	207	≤0.008	0.016	≤0.008-2.0
<i>Haemophilus parainfluenzae</i>	GGSS	56	0.015	0.03	0.001-0.12
	CAST	4	≤0.03	—	≤0.03
	CMI	101	0.016	0.06	≤0.008-4.0
<i>Moraxella catarrhalis</i>	GGSS	233	0.008	0.008	0.001-0.03
	Alexander Project	191	0.015	0.015	0.008-0.03
	CAST	263	≤0.004	0.008	≤0.004-0.015
	CMI (β-lactamase positive)	163	≤0.008	≤0.008	≤0.008-0.03
	CMI (β-lactamase negative)	18	≤0.008	≤0.008	≤0.008-0.016

TABLE 37
In vitro Activity of Gemifloxacin against *H. influenzae*, *H. parainfluenzae*
and *M. catarrhalis* Isolates from Surveillance Studies—All geographic regions

Organism	Study	Number of Isolates	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)	MIC Range (µg/mL)
<i>Haemophilus influenzae</i>	(GGSS)	1817	0.004	0.008	0.001-1.0
	Alexander Project	4188	0.008	0.03	0.008-0.5
	CAST	847	≤0.004	≤0.004	≤0.004-0.06
<i>Haemophilus parainfluenzae</i>	GGSS	320	0.015	0.03	0.001-0.12
<i>Moraxella catarrhalis</i>	GGSS	699	0.008	0.015	0.001-0.12
	Alexander Project	633	0.008	0.015	0.008-0.5

TABLES 38 to TABLE 40 show the frequency distribution of gemifloxacin and comparator MICs for *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and *Moraxella catarrhalis*. The tables present the data combined from all four surveillance studies. Only the data from all geographic regions is shown. All fluoroquinolones were active against these three species.

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TABLE 38
Frequency Distribution of MICs for *Haemophilus influenzae* in Surveillance Studies
(all geographic regions)

N/Cum%	0.001	0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	Total
Gemifloxacin	181 2.53	612 11.10	1162 27.36	3573 77.37	784 88.34	592 96.63	190 99.29	39 99.83	8 99.94	2 99.97	1 99.99	1 100			7145
Ciprofloxacin				512 7.30	5183 79.89	1138 95.83	52 96.55	17 96.79	201 99.61	11 99.76	13 99.94	1 99.96	3 100*		7140
Grepafloxacin				229 12.61	1492 94.77	46 97.30	21 98.46	13 99.17	10 99.72	3 99.89	1 99.94	1 100			1816
Levofloxacin				5 0.19	1544 57.69	1055 96.98	38 98.40	7 98.66	15 99.22	11 99.63	4 99.78	1 99.81	3 99.93	2 100*	2685
Ofloxacin				10 0.16	46 0.99	1321 22.23	4048 87.57	522 96.00	16 96.26	207 99.60	12 99.79	12 99.98	1 100		6195
Sparfloxacin				237 87.45	23 95.94	7 98.52	4 100								271
Trovafloxacin				381 12.89	1595 66.85	906 97.50	36 98.71	21 99.42	8 99.70	5 99.86	2 99.93			2 100*	2956

* Highest concentration tested in one or more of the studies.

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TABLE 39
Frequency Distribution of MICs for *Haemophilus parainfluenzae* in Surveillance Studies
(all geographic regions)

N/Cum%	0.001	0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	Total
Gemifloxacin	7 1.65	26 7.76	38 16.71	104 41.18	109 66.82	95 89.18	37 97.88	7 99.53		1 99.76			1 100		425
Ciprofloxacin				7 1.65	265 64.15	107 89.39	15 92.92	4 93.87	12 96.70	8 98.58	1 98.82	1 99.06	4 100*		424
Grepafloxacin				6 1.88	134 43.89	72 66.46	73 89.34	18 94.98	12 98.75	3 99.69	1 100				319
Levofloxacin					124 31.08	167 72.93	74 91.48	15 95.49	7 97.24	4 98.25	5 99.50	1 99.75	1 100		399
Ofloxacin				1 0.31		3 1.24	223 70.28	59 88.54	12 92.26	12 95.98	11 99.38		2 100		323
Sparfloxacin				7 26.92		7 53.85	11 96.15	1 100							26
Trovafoxacin				8 1.89	130 32.55	95 54.95	105 79.72	66 95.28	15 98.82	3 99.53		1 99.76		1 100*	424

* Highest concentration tested in one or more of the studies.

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TABLE 40
Frequency Distribution of MICs for *Moraxella catarrhalis* in Surveillance Studies
(all geographic regions)

N/Cum%	0.001	0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	Total
Gemifloxacin	7 0.38	24 1.69	247 15.14	1101 75.11	361 94.77	87 99.51	6 99.84	2 99.95		1 100					1836
Ciprofloxacin				7 0.38	254 14.22	1158 77.29	322 94.83	10 95.37	70 99.18	9 99.67	2 99.78	1 99.84	3 100*		1836
Grepafloxacin					619 91.84	37 97.33	8 98.52	3 98.96	4 99.55	1 99.70	1 99.85			1 100	674
Levofloxacin				2 0.17	33 2.91	935 80.63	207 97.84	8 98.50	9 99.25	4 99.58	4 99.92	1 100			1203
Ofloxacin					1 0.07	1 0.14	705 50.79	601 93.97	5 94.32	66 99.07	5 99.43	6 99.86	1 99.93	1 100*	1392
Trovafloxacin				108 8.98	729 69.58	344 98.17	9 98.92	5 99.33	5 99.75	1 99.83	1 99.92	1 100			1203

* Highest concentration tested in one or more of the studies.

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Figures 11 to 13 show the gemifloxacin data from the surveillance studies in bar graphs for *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and *Moraxella catarrhalis*. Only the data from all geographic regions combined is shown.

Figure 11—Frequency distribution of gemifloxacin MICs for *H. influenzae*
From surveillance studies—all geographic regions (n = 2,820)

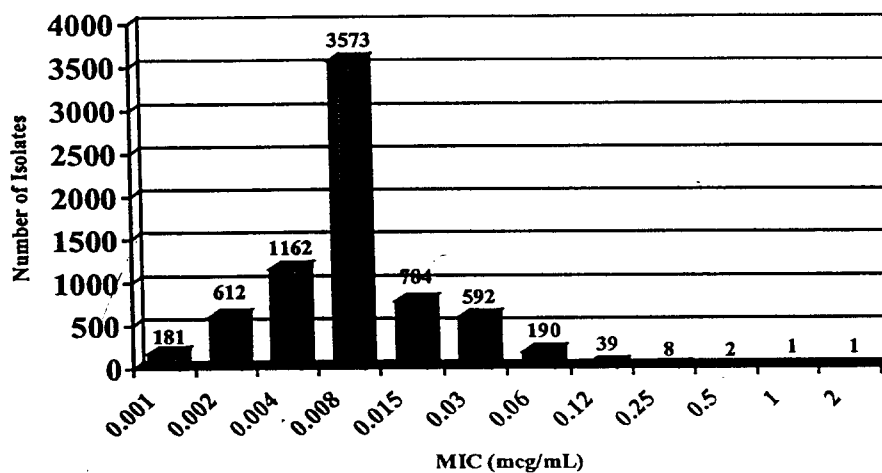
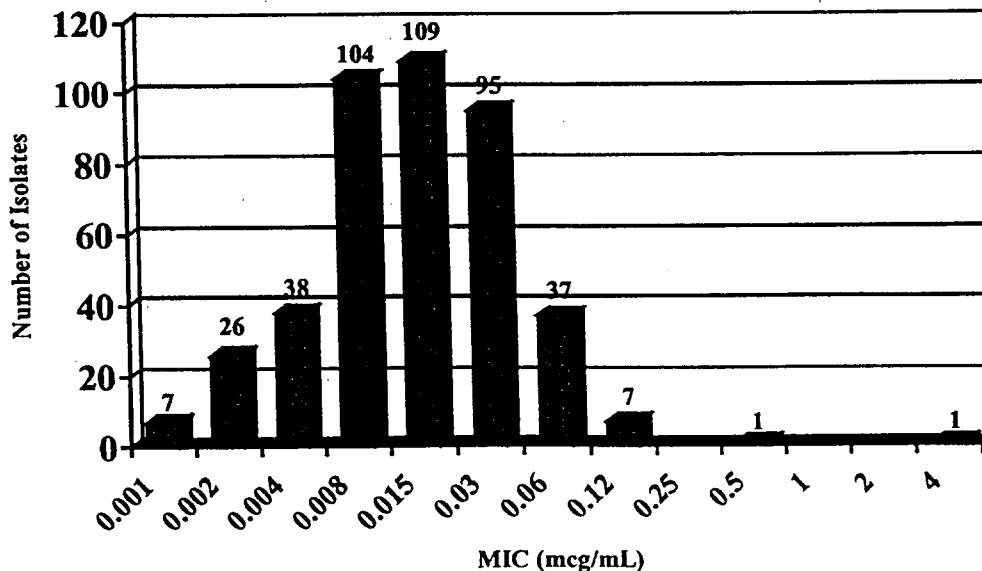


Figure 12—Frequency distribution of gemifloxacin MICs for *H. parainfluenzae*
From surveillance studies—all geographic regions (n = 425)



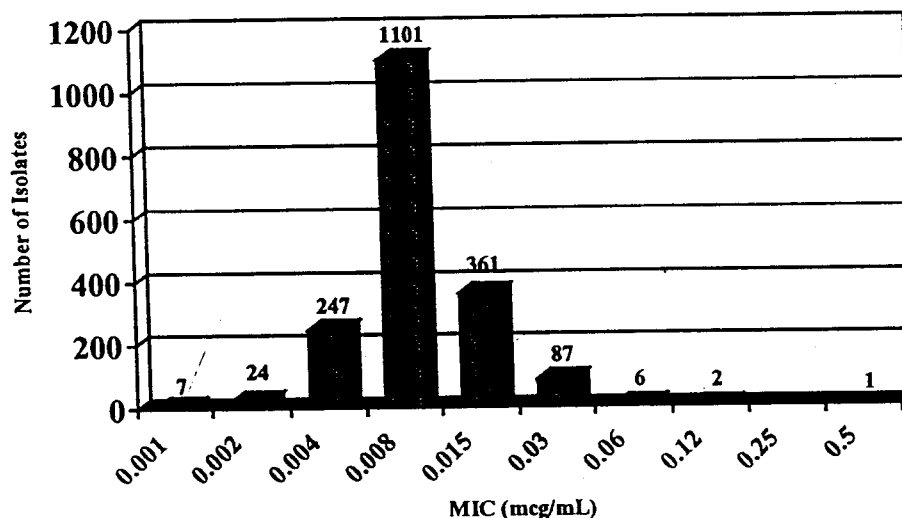
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Figure 13—Frequency distribution of gemifloxacin MICs for *M. catarrhalis*
From surveillance studies—all geographic regions (n = 1,836)



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Clinical data

This section contains frequency distributions of the gemifloxacin MICs for the *Haemophilus influenzae* isolated from the Intent to Treat population during the Phase III clinical studies. The MIC₉₀ for *H. influenzae* isolates recovered in North America and from all geographic regions was 0.008 µg/mL.

TABLE 41
Frequency Distribution of MICs for Gemifloxacin for *H. influenzae*
From the Phase III Clinical Studies (North America)

N=89	≤0.001	0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2
Gemi n	9	50	20	6	2	0	0	0	0	0	0	1
Cum %	10.1	66.3	88.8	95.3	97.8	97.8	97.8	97.8	97.8	97.8	97.8	100

TABLE 42
Frequency Distribution of MICs for Gemifloxacin for *H. influenzae*
From the Phase III Clinical Studies (all geographic regions)

N=297	≤0.001	0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	>256
Gemi n	38	137	77	21	11	4	2	1	0	0	0	1	1
Cum %	12.8	60.3	86.2	93.3	97.0	98.3	99.0	99.3	99.3	99.3	99.3	99.7	100 ¹

¹ MIC₁₀₀ = >256 µg/mL—it is likely this is a laboratory error

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Discussion

The studies outlined in this section demonstrate that gemifloxacin has good activity against *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and *Moraxella catarrhalis*.

The MIC₉₀ value for *H. influenzae* was ≤ 0.06 $\mu\text{g/mL}$. In most studies the MIC₉₀ was 0.008 or 0.016 $\mu\text{g/mL}$. Over 7000 isolates were tested with over 2500 isolates from North America. *Haemophilus influenzae* will be allowed in the label unless clinical efficacy is not proven.

The MIC₉₀ value for *H. parainfluenzae* was ≤ 0.12 $\mu\text{g/mL}$ in all studies. The overall MIC₉₀ value in the surveillance studies was 0.06 $\mu\text{g/mL}$. Over 400 isolates were tested with over 160 isolates from North America. *Haemophilus parainfluenzae* will be allowed in the label unless clinical efficacy is not proven.

The MIC₉₀ value for *M. catarrhalis* was ≤ 0.015 $\mu\text{g/mL}$ in all studies. Over 1800 isolates were tested with over 900 North American isolates. *Moraxella catarrhalis* will be allowed in the label unless clinical efficacy is not proven.

Other Gram-Negative Aerobes

To determine the activity of gemifloxacin against Gram-negative aerobes, other than *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and *Moraxella catarrhalis*, a number of *in vitro* susceptibility studies were conducted.

In vitro profile studies

Most studies demonstrated that gemifloxacin had variable *in vitro* activity against gram-negative organisms. Most species had MIC₉₀ values close to or at the susceptible breakpoint. The MIC₅₀ values in most studies were several dilutions lower than the MIC₉₀ values. The few studies that separated strains containing extended spectrum beta-lactamases (ESBLs) indicated that these strains were not susceptible to gemifloxacin. Certain species such as _____ and _____ species had MICs that were higher than for most other Enterobacteriaceae. In general the activity of gemifloxacin was equivalent to or one-dilution less than that of ciprofloxacin, but ciprofloxacin's susceptible breakpoint is 4 times higher.

A summary of these studies is shown in TABLE 43.

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TABLE 43
Summary of gemifloxacin and comparator activity against
Aerobic Gram-negative organisms from *in vitro* profile studies

Compound	No. of Isolates	MIC Range (µg/mL)	Range of MIC ₉₀ s (µg/mL)	Median MIC ₉₀ (µg/mL)	References
Gemifloxacin	828	≤0.002->16	0.03-0.25	0.03	[34][43]
Trovafoxacin	828	≤0.002->16	0.06-0.25	0.06	[34] [43]
Ciprofloxacin	828	≤0.002->8	0.015-0.25	0.015	[34] [43]
<i>K. pneumoniae</i>					
Gemifloxacin	535	≤0.008->16	0.25-8	0.5	[34] [35] [33] [43]
Clinafloxacin	50	≤0.008-1	1	NA ¹	[33]
Moxifloxacin	50	0.015-1	0.5	NA	[33]
Trovafoxacin	535	≤0.008->16	0.5-8	1	[34] [35] [33] [43]
Levofloxacin	70	0.015->16	0.5-1	0.5	[35] [33]
Ciprofloxacin	535	≤0.008->16	0.5->8	0.5	[34] [35] [33] [43]
Gemifloxacin	29	≤0.06->16	0.5	NA	[34]
Trovafoxacin	29	≤0.12->16	0.5	NA	[34]
Ciprofloxacin	29	≤0.06->8	0.25	NA	[34]
Gemifloxacin	245	≤0.03->64	0.25-16	0.25	[34] [35] [43]
Trovafoxacin	245	≤0.03->64	1-16	1	[34] [35] [43]
Levofloxacin	20	0.06->16	0.12	NA	[35]
Ciprofloxacin	245	≤0.03->64	0.06-16	0.06	[34] [35] [43]
Gemifloxacin	89	0.015->16	0.12-2	0.12	[34] [35]
Trovafoxacin	89	0.03->16	0.25-4	0.25	[34] [35]
Levofloxacin	20	0.03-2	0.25	NA	[35]
Ciprofloxacin	89	0.015-4	0.12-0.5	0.12	[34] [35]
Gemifloxacin	54	0.06->16	1-4	1	[34] [35]
Trovafoxacin	54	0.06->16	2->16	2	[34] [35]
Levofloxacin	20	0.03-4	0.5	NA	[35]
Ciprofloxacin	54	0.03->8	0.5-4	0.5	[34] [35]
Gemifloxacin	687	0.06->64	2->64	>16	[34] [59] [43]
Trovafoxacin	687	0.06->64	4->64	>16	[34] [59] [43]
Levofloxacin	200	0.03-64	4	NA	[59]
Ciprofloxacin	687	0.015->64	1-64	>8	[34] [59] [43]
Gemifloxacin	19	4-64	64	NA	[35] [59]
Trovafoxacin	19	8->64	>64	NA	[35] [59]
Levofloxacin	19	8-64	64	NA	[35] [59]
Ciprofloxacin	19	2-32	32	NA	[35] [59]

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TABLE 43 (continued)
Summary of gemifloxacin and comparator activity against
Aerobic Gram-negative organisms from *in vitro* profile studies

Compound	No. of Isolates	MIC Range (µg/mL)	Range of MIC ₉₀ s (µg/mL)	Median MIC ₉₀ (µg/mL)	References
Gemifloxacin	26	0.03-4	1	NA	[35]
Trovaflaxacin	26	0.06-4	1	NA	[35]
Levofloxacin	26	0.06-4	2	NA	[35]
Ciprofloxacin	26	0.03-2	1	NA	[35]
Gemifloxacin	20	0.25-16	2	NA	[35]
Trovaflaxacin	20	0.12-16	2	NA	[35]
Levofloxacin	20	0.5-16	4	NA	[35]
Ciprofloxacin	20	1->16	8	NA	[35]
Gemifloxacin	160	≤0.03-32	16	NA	[75]
Trovaflaxacin	160	≤0.03-32	16	NA	[75]
Levofloxacin	160	≤0.03-32	16	NA	[75]
Ciprofloxacin	160	≤0.03->125	128	NA	[75]
Gemifloxacin	234	≤0.12->16	>16	NA	[34]
Trovaflaxacin	234	≤0.12->16	>16	NA	[34]
Ciprofloxacin	234	≤0.06->8	>8	NA	[34]
Gemifloxacin	20	0.008-0.25	0.06	NA	[35]
Trovaflaxacin	20	0.008-0.25	0.12	NA	[35]
Levofloxacin	20	0.03-1	0.25	NA	[35]
Ciprofloxacin	20	0.008-1	0.5	NA	[35]

¹ NA = Not applicable—insufficient data to determine a median value

² Includes

TABLES 44 to 65 shows the results of individual profile studies for some important Gram-negative organisms. Individual tables have been included for each of the organisms the sponsor has included in the proposed label. Individual tables have also been included for a few of the more common Gram-negative organisms that have high gemifloxacin MIC values and have not been included in the sponsor's proposed label. As is evident from these tables, gemifloxacin's activity is variable for most of these species. In almost all species many MIC₉₀ values are close to the proposed susceptible breakpoint of 0.25 µg/mL. Most species had numerous studies with high MIC₉₀ values.

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TABLE 44
Activity of Gemifloxacin Against

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TABLE 45
Activity of Gemifloxacin Against
Acinetobacter lwoffii (individual studies)

Compound	No. of Isolates	Country	MIC Range ($\mu\text{g/mL}$)	MIC ₅₀ ($\mu\text{g/mL}$)	MIC ₉₀ ($\mu\text{g/mL}$)	Reference
Gemifloxacin	7	CMI	$\leq 0.008-0.06$	0.016	---	[31]
Gemifloxacin	124	Global	0.001-16	0.03	0.25	[28]

Over 100 isolates have been tested and more than one study has been performed. The MIC₉₀ values are below the susceptible breakpoint. *Acinetobacter lwoffii* may remain in the *in vitro* activity listing.

TABLE 46
Activity of Gemifloxacin Against

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TABLE 52
Activity of Gemifloxacin Against
Klebsiella pneumoniae (individual studies)

Compound	No. of Isolates	Country	MIC Range (µg/mL)	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)	Reference
Gemifloxacin	50	Italy	≤0.008-1	0.03	0.25	[33]
	20 ESBL +		0.03-1	0.25	0.25	
	30 ESBL -		≤0.008-0.12	0.015	0.06	
Gemifloxacin	409	USA	≤0.03-≥16	0.06	0.25	[34]
Gemifloxacin	20	USA	0.008-≥16	0.06	0.25	[35]
Gemifloxacin	56	Greece	≤0.03-4	0.06	0.25	[43]
Gemifloxacin	20	USA	0.015-≥8	0.03	0.12	[46]
Gemifloxacin	45	Korea	0.016-1	0.06	0.25	[51]
Gemifloxacin	45	Korea	0.016-2	0.12	0.25	[52]
Gemifloxacin	20	Korea	0.03-8	0.06	0.25	[53]
Gemifloxacin	149	USA	0.008-32	0.03	0.25	[57]
Gemifloxacin	255	CMI	≤0.03-≥16	0.06	0.25	[31]
Gemifloxacin	1820	Global	0.002-≥256	0.03	0.25	[28]
	282	USA	---	0.03	0.25	

Shaded values are above gemifloxacin susceptible breakpoint

Several studies have high MIC₉₀ values. Most of the other studies had MIC₉₀ values of 0.25 µg/mL (breakpoint concentration). This species is included in the clinical efficacy section of the label. If clinical efficacy is not shown then it must be eliminated from the label.

TABLE 53
Activity of Gemifloxacin Against
Klebsiella oxytoca (individual studies)

Compound	No. of Isolates	Country	MIC Range (µg/mL)	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)	Reference
Gemifloxacin	26	USA	≤0.03-≥16	≤0.03	0.25	[39]
Gemifloxacin	10	USA	0.016-0.06	0.03	0.03	[46]
Gemifloxacin	48	Korea	0.03-0.06	0.06	0.06	[52]
Gemifloxacin	59	USA	0.008-8	0.016	0.25	[57]
Gemifloxacin	103	CMI	≤0.008-8	0.03	0.25	[31]
Gemifloxacin	710	Global	0.002-8	0.03	0.06	[28]
	126	USA	---	0.015	0.25	

Over 100 isolates were tested. More than one study was performed. All MIC₉₀ values were ≤0.25 µg/mL. *Klebsiella oxytoca* may remain in the *in vitro* activity listing in the label.

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TABLE 56
Activity of Gemifloxacin Against
Proteus vulgaris (individual studies)

Compound	No. of Isolates	Country	MIC Range (µg/mL)	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)	Reference
Gemifloxacin	20	USA	0.06-0.25	0.12	0.25	[35]
Gemifloxacin	10	USA	0.03-0.5	0.03	0.12	[46]
Gemifloxacin	20	Korea	0.03-0.25	0.06	0.06	[52]
Gemifloxacin	12	Korea	0.12->8	0.25	0.25	[53]
Gemifloxacin	25	CMI	≤0.008-1	0.06	0.25	[31]
Gemifloxacin	424	Global	0.004-8	0.12	0.25	[28]
	23	USA	—	0.06	0.12	

Shaded values are above gemifloxacin susceptible breakpoint

Over 100 isolates have been tested. Only one small Korean study had a MIC₉₀ value greater than 0.25 µg/mL. *Proteus vulgaris* may remain in the *in vitro* listing.

TABLE 57
Activity of Gemifloxacin Against

Activity of Gemifloxacin Against

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TABLE 65
Activity of Gemifloxacin Against

Surveillance Studies

TABLE 66 and TABLE 67 show gemifloxacin MIC₅₀, MIC₉₀, and range for
_____ *Klebsiella pneumoniae*, _____

_____ *Acinetobacter lwoffii*, _____

_____ isolates tested from The Global

Gemifloxacin Surveillance Study (GGSS) (28), CAST (30), and CMI (31). The range of MIC₉₀s for _____ in the US/Canada was ≤ 0.03 -0.03 $\mu\text{g/mL}$ and 0.06-0.25 $\mu\text{g/mL}$ for all geographic regions. The range of MIC₉₀s for _____ in the US/Canada was 0.25-2.0 $\mu\text{g/mL}$ and was 4-8 $\mu\text{g/mL}$ for all geographic regions. The range of MIC₉₀s for *K. pneumoniae* in the US/Canada was 0.25-0.5 $\mu\text{g/mL}$ and was 0.5 $\mu\text{g/mL}$ for all geographic regions. The range of MIC₉₀s for _____ in the US/Canada and all geographic regions was 0.25-0.5 $\mu\text{g/mL}$. The range of MIC₉₀s for _____ s in the US/Canada was 0.25 $\mu\text{g/mL}$ and 4.0-16.0 $\mu\text{g/mL}$ for all geographic regions. Some isolates outside of the US/Canada had higher MIC values and these caused the MIC₉₀ values to be higher in these foreign studies. Gemifloxacin was much less active against _____ and the _____ listed in the table with the exception of *A. lwoffii* with a MIC₉₀ range of ≤ 0.03 -0.06 $\mu\text{g/mL}$ in the US/Canada and 0.25 $\mu\text{g/mL}$ for all geographic regions. There were no significant differences in the activity of gemifloxacin against isolates collected in Europe and those collected in North America except for _____ and *K. pneumoniae*, which had MIC₉₀s of ≤ 0.25 $\mu\text{g/mL}$ in North America, but > 0.25 $\mu\text{g/mL}$ in Europe.

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TABLE 66
In vitro Activity of Gemifloxacin against Gram-Negative
Isolates from Surveillance Studies—US/Canada

Organism	Study	Number of Isolates	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)	MIC Range (µg/mL)
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<i>Klebsiella pneumoniae</i>	GGSS	282	0.03	0.25	0.002-256
	CAST	263	<0.03	0.25	≤0.03->4
	CMI	255	0.03	0.5	<0.008-8

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<i>Acinetobacter lwoffii</i>	GGSS	11	0.03	0.06	0.004-0.5
	CAST	4	≤0.03	NA*	≤0.03
	CMI	7	0.016	NA	≤0.008-0.06

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